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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,892	GOLZ ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *12-24 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 25* is/are rejected.

7)☒ Claim(s) *1-3* is/are objected to.

8)☒ Claim(s) *1-26* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/22/04; 5/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence Alignment #1*.

DETAILED ACTION

Election/Restrictions

Applicants' election of Group I, claims 1-11, in the reply filed on 7/2/07 is acknowledged. Applicants did not indicate whether the election was with or without traverse. However, because Applicants did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

As set forth at pg 3 of the 6/13/07 restriction requirement, claim 25 is a linking claim that links Groups I and VII. Therefore, the restriction requirement between the linked groups (I and VII) is subject to nonallowance of linking claim 25. For the reasons set forth below claim 25 has not been allowed; therefore, the restriction requirement between Groups I and VII is maintained.

Claims 12-24 and 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicants were required to elect a single species of disease. Applicants' election of the species of "cardiovascular diseases" in the reply filed on 7/2/07 is acknowledged. Each of claims 1-11 and 25 encompasses this species.

Claims 1-11 and 25 are under consideration, as they read upon the elected species of "cardiovascular diseases".

Claim Objections

Claims 1-3 are objected to because of the following informalities:

(1) Claims 1-3 are objected to because the word "and" should be placed between method steps (i) and (ii) in each of these claims.

(2) Claim 3 is also objected to because the phrase "at the presence of a compound" is grammatically awkward. The phrase could be corrected, for example, by amending the phrase to recite, "in the presence of a compound".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of screening for an agent that binds to, or regulates the activity of, the NPFF1 receptor. The identified agents are to be used to treat any of seven different species of disease (recited as a Markush-type group in the preamble of each of independent claims 1-3 and 25). The elected species of disease under consideration is "cardiovascular diseases". It is noted that the intended use of "therapeutic agents useful in the treatment of ... cardiovascular diseases ... in a mammal" (as recited in the preamble of the independent claims) bears no accorded patentable weight to distinguish a claimed method over one from the prior art. However, said intended use must still meet the requirements of 35 U.S.C. 112, 1st paragraph (i.e., the specification must enable the skilled artisan to use the claimed method for the use recited in the preamble). For the reasons set forth below, the specification does not enable the skilled artisan to use the claimed method to identify a therapeutic agent

useful in the treatment of a cardiovascular disease. As such, the specification does not provide enablement for any embodiment directed to the elected species of disease. As the elected species is not allowable, the other species of disease recited in the Markush-type group have not been considered.

The breadth of the claims is extremely large in several respects, even when the claims are considered only in view of the elected species of disease. First, the claims encompass methods to identify therapeutic agents for any type of "cardiovascular disease". The specification teaches that such diseases include a large genus of different conditions including congestive heart failure, myocardial infarction (heart attack), ischemic diseases such as angina, atrial and ventricular arrhythmias, hypertensive vascular diseases, peripheral vascular diseases, and atherosclerosis (pg 55, line 13 to page 57, line 16). Second, the claims encompass methods of screening with a large genus of NPFF1 polypeptide variants that are not limited with respect to structure or function. Third, the claims encompass identification of therapeutic agents based on either binding to NPFF1 (claims 1 and 4-11) or by modulation of any "activity" of the NPFF1 polypeptide (claims 2, 3, and 25). Fourth, while all of the claims encompass *in vitro* methods of screening, claims 1-4, 7-9 and 25 also encompass *in vivo* methods of screening, for example those performed using transgenic animals.

In contrast to the breadth of the claims, the specification provides limited teachings in support of the claimed invention. Example 1 describes a nucleic acid encoding NPFF1 that has 100% identity with several known sequences. The specification further teaches a single NPFF1 polypeptide of SEQ ID NO: 2 (430 amino acids) and describes this protein as a member of the family of G-protein coupled receptors (GPCRs). Example 2 describes the relative expression of NPFF1 mRNA in 91 different tissues; as shown in Table 1, NPFF1 mRNA could be detected in 90 tissues, with the highest levels in the right cerebellum, left cerebellum, total cerebellum, dorsal root ganglia, postcentral gyrus, thalamus, tonsilla cerebelli, cervix, parietal lobe, Alzheimer brain frontal lobe, cerebral peduncles, prostate BPH, aorta, vermis cerebelli and rectum. Examples 3-14 are prophetic examples describing further experiments that could be conducted with NPFF1; however, no results specific to NPFF1 are disclosed.

Example 3 teaches that antisense nucleotides can be used to ascertain gene function. Example 4 describes vectors and host cells that can be used for protein expression. Example 5 teaches that recombinant proteins can be purified following expression. Example 6 describes prior art experiments with chimeric GPCRs; however, no results with a chimeric NPFF1 are disclosed. Example 7 describes two approaches for raising antibodies to proteins. Example 8 teaches that antibodies can be used in disease diagnosis; however, no specific diseases associated with NPFF1 are disclosed. Example 9 describes methods for purification of proteins from biological samples. Example 10 describes possible methods for screening for agonists or antagonists of GPCR activity using second messenger systems commonly associated with GPCRs including adenylate cyclase, calcium mobilization or inositol phosphate hydrolysis; however, no specific GPCR activities are taught for NPFF1. Example 11 describes "rational drug design" approaches for designing structural analogs of biologically active polypeptides or ligands thereof. Example 12 describes general screening assays to identify binding partners of proteins. Example 13 describes general methods of administration of antibodies and other modulating compounds; no specific diseases associated with NPFF1 are disclosed. Example 14 describes general methods for production of non-human transgenic animals; no results are described indicating that transgenic NPFF1 animals were actually produced.

The prior art also provides limited teachings in support of the claimed invention. The prior art describes an NPFF2 polypeptide; specifically, Bonini et al (2000. Journal of Biological Chemistry. 275(50): 39324-39331). Bonini et al (2000) teach a human NPFF1 protein that consists of 430 amino acids and is identical to instant SEQ ID NO: 2 (see Sequence Alignment #1 attached to this Office Action). Bonini et al further teach a two GPCR-related activities for NPFF1. First, Bonini et al teach that, "[i]n COS-7 cells transfected with rat NPFF1 receptor, NPFF elicited a small (2-fold) increase in total inositol phosphate release ... which most likely reflects a minor activation of this pathway ... [w]hen NPFF1 was co-expressed with the $G\alpha_{q/z5}$, NPFF stimulation resulted in a much more robust inositol phosphate release response..." (pg 39327). Second, Bonini et al teach that, "[c]o-transfection of ... rat NPFF1 receptor with either $G\alpha_{q/i3}$ or

$G\alpha_{q/z5}$ led ... to the activation by NPFF [neuropeptide FF] of intracellular Ca^{2+} mobilization in a concentration-dependent manner (Fig. 5)" (pg 39327). Bonini et al further teach one other ligand (PQRF-amide) that can induce calcium mobilization in cells expressing human NPFF1. Bonini et al do not teach any other activities for NPFF1. Furthermore, Bonini et al do not teach an association between either NPFF1 activity and a cardiovascular disease.

In view of the teachings of the specification and the prior art, the skilled artisan could use an NPFF1 polypeptide of SEQ ID NO: 2 in a method of screening to identify a modulator of the inositol phosphate release or calcium mobilization of said protein. However, the claimed methods lack enablement for the following reasons:

(1) The claimed methods lack enablement for the intended use of identifying "therapeutic agents useful in treatment of ... cardiovascular diseases .. in a mammal" (each independent claim (claim 1-3 and 25) recites this intended use in the preamble of the claim). However, based on the limited teachings of the specification and prior art, the skilled artisan would not be able to predict whether or not a modulator of the calcium mobilization produced by an NPFF1 polypeptide could be used to treat a cardiovascular disease. Neither the specification nor the prior art teach provide any reasonable correlation between NPFF1 activity and a cardiovascular disease. The specification states, "NPFF1 is highly expressed in different cardiovascular related tissues such as heart, aorta, sclerotic aorta, and vein. The expression in the above mentioned tissues suggests an association between NPFF1 and cardiovascular diseases. NPFF1 can be regulated in order to treat or to diagnosis cardiovascular disorders" (pg 57, lines 13-16). However, the skilled artisan would recognize that gene expression in a particular tissue does not necessarily indicate that the encoded protein has a role in a disease associated with said tissue. A gene can be expressed in a tissue without having a role in a particular disease associated with that tissue. As shown by Applicants' working examples, NPFF1 is expressed in a wide variety of tissues, with the highest levels of expression in many tissues other than heart, aorta or vein. However, it is possible that NPFF1 activity has a role in said tissues that is entirely unrelated to any disease associated with said tissues. The relevant art teaches that thousands of different genes

are expressed in tissues of the cardiovascular system (see pg 689 of Juhasz et al, 2002. European Journal of Heart Failure. 4: 687-697; specifically, "a large profile of cDNAs obtained from 13 cardiovascular cDNA libraries, containing a total of 84,904 expressed sequence tags ... [t]his number has rapidly increased since that time"). The skilled artisan could not predict which, if any, of these expressed genes is associated with one or more cardiovascular diseases. Even if a particular gene is found to have a role in healthy tissue (e.g. healthy heart tissue), the skilled artisan could not predict whether or not it would also have a role in a cardiovascular disease, such that modulating its activity would treat said disease. As such, the it is not predictable whether or not a modulator of NPFF1 activity could be used to treat one or more cardiovascular diseases. Furthermore, the specification provides no guidance as to whether an agonist or an antagonist of NPFF1 would provide therapeutic treatment for a cardiovascular disease. In order to use the claimed method to identify a therapeutic, the skilled artisan would need to first practice the claimed method to identify a modulator of NPFF1 activity, and then engage in further experimentation to test whether or not the modulator could be used to treat one or more cardiovascular diseases.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification whether or not a regulator of NPFF1 could be used to treat one or more cardiovascular diseases. There are no examples of treatment of a cardiovascular disease with a regulator of NPFF1. There are no examples that connect NPFF1 activity with any cardiovascular disease. Thus the specification fails to teach the skilled artisan how to use the claimed methods to identify a therapeutic agent for a cardiovascular disease without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the claimed methods for the above stated purpose. Due to the large quantity of experimentation necessary to determine if whether or not a whether or not a regulator of NPFF1 could be used to treat one or more cardiovascular diseases, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the

teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention.

(2) Even if the claimed methods were enabled for a method of screening to identify a therapeutic using a polypeptide of SEQ ID NO: 2, they would lack enablement for a method of screening using other variants of SEQ ID NO: 2. Each of claims 1-11 and 25 encompasses use of a genus of variant "NPFF1" polypeptides. The genus of NPFF1 polypeptides encompassed by the claims is highly variant because a significant number of structural differences between genus members are permitted. The claims place no limitation on the structure or function of the NPFF1 polypeptide to be used in the claimed methods. The specification discloses a single human NPFF1 polypeptide of SEQ ID NO: 2 that consists of 430 amino acids, and is encoded by the nucleic acid of SEQ ID NO: 1. The specification teaches that an "NPFF1 polypeptide" includes a polypeptide of SEQ ID NO: 2 as well as variants which show at least 80% homology to SEQ ID NO: 2, and wherein said polypeptide "has NPFF1 activity" (pg 9, lines 1-15). As the polypeptide of SEQ ID NO: 2 consists of 522 amino acids, a variant with 80% homology has 86 amino acids that differ from SEQ ID NO: 2. Therefore, the genus of polypeptides contemplated by the specification includes those with one or more (up to 86) changes to the amino acid sequence of SEQ ID NO: 2 (including additions, deletions, or substitutions) and which retain an "NPFF1 activity".

None of the claims include the limitation that the polypeptide variants exhibit an activity of the parent polypeptide of SEQ ID NO: 2. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible variants of polypeptides of SEQ ID NO: 2. The specification has not provided a working example of the use of a variant of the polypeptide of SEQ ID NO: 2, nor sufficient guidance so as to enable one of skill in the art to make such a variant. The specification has failed to teach which amino acids of SEQ ID NO: 2 could be modified so as to produce a polypeptide that is not identical to SEQ ID NO: 2 and yet still retain a characteristic of the parent polypeptide. Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the

protein corresponding to SEQ ID NO: 2 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 2 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 2, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 2. Conversely, if a protein variant of SEQ ID NO: 2 need not have a disclosed property; the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified

in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Due to the large quantity of experimentation necessary to generate the large number of variants encompassed by the claimed methods and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(3) Even if the claimed methods were enabled for a method of screening to identify a therapeutic modulator of NPFF-induced inositol phosphate release or calcium mobilization activity of NPFF1 (as taught by Bonini et al (2000)), the claimed methods would lack enablement for methods of screening by identifying compounds that bind to an NPFF1 polypeptide (as encompassed by claims 1 and 4-11) or for compounds that modulate any "activity" of NPFF1 (as encompassed by claims 2, 3 and 25).

The fact that a test compound can bind to an NPFF1 polypeptide does not allow the skilled artisan predict whether or not said binding partner can also alter an activity of the NPFF1 polypeptide. A test compound can bind to a receptor without altering its activity. The skilled artisan would still need to test said binding partner in an assay that measured the ability of the binding partner to modulate NPFF1 activity. Furthermore, neither the specification nor the prior art teaches an activity for NPFF1 other than NPFF-induced inositol phosphate release or calcium mobilization activity. The specification teaches, "NPFF1 activity can be measured, for example, using methods described in the specific examples, below" (pg 48, lines 17-18). However, the specific examples described in specification do not teach any other particular activity for NPFF1. Example 10 describes possible methods for screening for agonists or antagonists of GPCR activity using second messenger systems commonly associated with GPCRs including adenylate cyclase, calcium mobilization or inositol phosphate hydrolysis; however, no specific GPCR activities are taught for NPFF1. As described above, Bonini et al (2000) provide support for NPFF-induced calcium mobilization and inositol phosphate release activities for NPFF1, but these two specific activities do not provide support for the genus of potential activities encompassed by the recited term "activity". Such a genus broadly includes any potential activity that a protein can be involved in. Significant further research would be necessary to determine whether or not NPFF1 possess any activities other than NPFF-induced calcium mobilization and inositol phosphate release. As such, the claims lack enablement for a method of screening for a regulator of any NPFF1 activity other than NPFF-induced inositol phosphate release or calcium mobilization (as taught by the prior art).

(4) Even if the claimed methods were enabled for a method of *in vitro* screening to identify a therapeutic for a cardiovascular disease, claims 1-4, 7-9 and 25 would lack enablement for *in vivo* methods of screening. Claims 1-4, 7-9 and 25 encompass a method of screening wherein the NPFF1 polypeptide is expressed *in vivo*, such as in a transgenic animal expressing SEQ ID NO: 2. The specification clearly contemplates transgenic animals with cells exogenously expressing the polypeptides of the invention (Example 14; pg 100-101). However, there are no methods or working examples

disclosed in the instant application whereby a multicellular animal with an NPFF1 gene is demonstrated to express the encoded peptide. The unpredictability of the art is very high with regards to making transgenic animals. For example, Wang et al (Nucleic Acids Research. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood. 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9%) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183).

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the disclosed protein, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that establishes the unpredictability of making transgenic animals, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-11 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

Each of claims 1-11 and 25 is a genus claim that encompasses use of a genus of variant "NPFF1" polypeptides. The genus of NPFF1 polypeptides encompassed by the claims is highly variant because a significant number of structural differences between genus members are permitted. The claims place no limitation on the structure or function of the NPFF1 polypeptide to be used in the claimed methods. The specification discloses a single human NPFF1 polypeptide of SEQ ID NO: 2 that consists of 430 amino acids, and is encoded by the nucleic acid of SEQ ID NO: 1. The specification teaches that an "NPFF1 polypeptide" includes a polypeptide of SEQ ID NO: 2 as well as variants which show at least 80% homology to SEQ ID NO: 2, and wherein said polypeptide "has NPFF1 activity" (pg 9, lines 1-15). As the polypeptide of SEQ ID NO: 2 consists of 430 amino acids, a variant with 80% homology has 86 amino acids that differ from SEQ ID NO: 2. Therefore, the genus of polypeptides contemplated by the specification includes those with one or more (up to 86) changes to the amino acid sequence of SEQ ID NO: 2 (including additions, deletions, or substitutions) and which retain an "NPFF1 activity". Thus, the claims are drawn to a genus of polypeptides defined only by sequence similarity. However, the instant specification fails to describe the entire genus of polypeptides that are encompassed by each of these claims.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides to be used in the claimed methods. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish the polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no

description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides to be used in the claimed methods. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a methods of screening comprising use of a polypeptide of SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the limitation "the cell" in line. There is insufficient antecedent basis for this limitation in the claim. Specifically, claim 5 depends from claim 1 and recites "wherein the cell is in vitro". However, the method of claim 1 does not recite a cell. As such, the recitation of "the cell" in claim 5 lacks antecedent basis in claim 1. For purposes of prosecution, the method of claim 5 will be interpreted to broadly encompass a method of claim 1 wherein the polypeptide is expressed in an in vitro cell.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonini et al, 2000. Journal of Biological Chemistry. 275(50): 39324-39331.

The elected species of disease under consideration is "cardiovascular diseases". The recitation of "screening for therapeutic agents useful in the treatment of ... cardiovascular diseases ... in a mammal" in the preamble of the claims from the instant application is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed method over one from the prior art. See MPEP 2111.02, "Effect of Preamble", section II, "Preamble Statements Reciting Purpose or Intended Use".

Therefore, the method of claim 1 encompasses a method of screening comprising contacting a test compound with a NPFF1 polypeptide and detecting binding of said test compound to said NPF2 polypeptide. Bonini et al (2000) teach a human NPFF1 polypeptide (see Figure 1) that is 100% identical to residues 1-430 of instant SEQ ID NO: 2 (an alignment of the two sequences is attached to this Office Action as Sequence Alignment #1). Bonini et al further teach, "Membranes from transiently transfected COS-7 cells exhibited high affinity, saturable [I^{125}]1DMeNPFF binding for both NPFF1 and NPFF2" (pg 39327). As such, Bonini et al teach a method of contacting a test compound ([I^{125}]1DMeNPFF) with a NPFF1 polypeptide and detecting binding of said test compound to said NPFF1 polypeptide. Therefore, Bonini et al teach a method that anticipates instant claim 1.

The method of claim 2 encompasses a method of screening comprising determining the activity of a NPFF1 polypeptide a certain concentration of a test compound or in the absence of said test compound, and determining the activity of said polypeptide at a different concentration of said test compound. No limitation is placed on the type of activity. Bonini et al further teach, "[c]o-transfection of rat NPFF1 or human NPFF2 receptors with either $G\alpha_{q/i3}$ or $G\alpha_{q/z5}$ led, in both cases, to the activation of NPFF of intracellular Ca^{2+} mobilization in a concentration-dependent manner (Fig. 5)" (pg 39327). As indicated, Figure 5A shows a comparison of the activity of NPFF1 at various concentrations of the test compound NPFF. As such, Bonini et al teach a method that anticipates instant claim 2.

The method of claim 3 encompasses a method of screening comprising determining the activity of a NPFF1 polypeptide at a certain concentration of a test compound, and determining the activity of said NPFF1 polypeptide at the presence of a

compound known to be a regulator of a NPFF1 polypeptide. Table II of Bonini et al demonstrates the activity of two compounds (FPP and PQRF-amide) in comparison to NPFF. PQRF-amide acts as an agonist of the NPFF1 receptor with a higher EC_{50} and lower response than NPFF. Therefore, Bonini teaches a method comprising determining the activity of NPFF1 polypeptide at a certain concentration of a test compound (PQRF-amide) and determining the activity of said NPFF1 polypeptide at the presence of a compound known to be regulator of a NPFF1 polypeptide (NPFF, known to be a regulator of NPFF1 in view of the results of Figure 5). As such, Bonini et al teach a method that anticipates instant claim 3.

Claim 4 depends from claim 1 and limits the contacting step to "in or at the surface of a cell". Bonini further teaches binding assays using the human NPFF1 receptor expressed in HEK-293 cells (pg 39327). The NPFF1 receptor is a cell membrane expressed GPCR; therefore, the contacting step occurs at the cell surface. As such, the teachings of Bonini et al also anticipate claim 4.

Claim 5 depends from claim 1 and limits the method by reciting, "wherein the cell is in vitro". As noted in the section titled, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", this claim lacks antecedent basis for the recitation of "the cell" because the method of claim 1 does not refer to a cell. For purposes of prosecution, the method of claim 5 has been interpreted to broadly encompass a method of claim 1 wherein the polypeptide is expressed in an *in vitro* cell. As described above, Bonini et al perform binding assays with NPFF1 expressed in HEK-293 cells, which are an isolated *in vitro* cell line. As such, the teachings of Bonini et al described above also anticipate claim 5.

Claim 6 depends from claim 1 and limits the method to one wherein "the step of contacting is in a cell-free system". As described above for claim 1, Bonini et al teach binding assays using membranes from COS-7 cells. Isolated cell membranes meet the definition of a "cell-free system". As such, the teachings of Bonini et al described above also anticipate claim 6.

Claim 7 depends from claim 1 and limits the method to one wherein "the polypeptide is coupled to a detectable label". The phrase "coupled" broadly encompasses any form of binding, and the phrase "detectable label" encompasses a

radiolabeled ligand. As such, the binding assays described by Bonini et al, wherein a radiolabeled ligand binds to the NPFF1 receptor, meet the definition of a coupling to a detectable label. As such, the teachings of Bonini et al described above also anticipate claim 7.

Claim 8 depends from claim 1 and limits the compound to a compound coupled to a detectable label. As described above, the NPFF test compound used by Bonini et al is coupled to a detectable [I^{125}] label. As such, the teachings of Bonini et al described above also anticipate claim 8.

Claim 9 depends from claim 1 and limits the method to one wherein, "the test compound displaces a ligand which is first bound to the polypeptide". Bonini further teaches, competition binding assays wherein several ligands are test for the ability to displace the ligand [I^{125}]1DMeNPFF (see Table I on pg 39328). As such, the teachings of Bonini et al described above also anticipate claim 9.

Claims 10 and 11 each depend from claim 1 and respectively limit the method to one wherein, "the polypeptide is attached to a solid support" (claim 10) or "the compound is attached to solid support". The claims do not limit the step at which the polypeptide is attached to a solid support; therefore, the claim broadly encompasses a method wherein the polypeptide or compound is attached to a solid support after incubation with the ligand. Furthermore, the claims encompass direct or indirect (e.g., via another compound) attachment. The membrane binding assays conducted by Bonini et al result in both the membrane-bound receptor and ligand being deposited on a "double layer of glass fiber filters" (pg 39325), which are used for scintillation counting to measure the quantity of radiolabeled ligand that bound to the receptor. Glass fiber filters meet the definition of a solid support. Therefore, Bonini et al teach a binding assay which results in the NPFF1 polypeptide and the radiolabeled NPFF ligand each being attached to a solid support. As such, the teachings of Bonini et al described above also anticipate each of claims 10 and 11.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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